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Self-Reflection and the Psychosis-Prone Brain: An fMRI Study

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Objective: The Cortical Midline Structures (CMS) play a critical role in self-reflection, together with the insula. Abnormalities in self-referential processing and its neural underpinnings have been reported in schizophrenia and at-risk populations, suggesting they might be markers of psychotic vulnerability. Psychometric measures of schizotypal traits may be used to index *psychosis proneness* (PP) in nonclinical samples. It remains an unresolved question whether differences in self-reflective processing are associated with PP. **Method:** Six hundred students completed the Community Assessment of Psychic Experiences Questionnaire, positive subscale. Two groups were formed from the extremes of the distribution (total $N = 36$). fMRI was used to examine CMS/insula function during a self-reflection task. Participants judged personality trait sentences about self and about an acquaintance. **Results:** High PP subjects attributed less positive traits to others (i.e., acquaintances) than subjects with low PP. Across groups, the contrasts self > semantic and self > other induced activation in CMS and insula, whereas other > semantic did not produce insula activation. Other > self induced posterior cingulate cortex activation in low PP but not in high PP. In addition, high PP subjects showed stronger activation than low PP in left insula during self > semantic. Examining valence effects revealed that high PP individuals showed increased activation in left insula, right dMPFC, and left vMPFC for positive self-related traits, and in bilateral insula, ACC, and right dMPFC for negative self-related traits. **Conclusions:** The findings suggest that aspects of self-referential processing and underlying brain mechanisms are similar in clinical and subclinical (high PP) forms of psychosis, suggesting that these may be associated with vulnerability to psychosis.

Keywords: psychosis proneness, fMRI, self-reflection, insula, prefrontal cortex, cortical midline, cingulate

Functional neuroimaging research has revealed a set of regions located in the midline of the human cerebral cortex (Cortical Midline Structures, CMS), encompassing the posterior cingulate cortex (PCC), anterior cingulate cortex (ACC), and medial pre-

frontal cortex (MPFC), which are engaged during self-reflective processes (Gusnard, Akdubak, Shulman, & Raichle, 2001; Kelley et al., 2002; Northoff et al., 2006; van der Meer, Costafreda, Aleman, & David, 2010). These findings have led to the hypothesis that activity within this network represents a plausible substrate for maintaining an integrated sense of self (Northoff, & Bermpohl, 2004). Besides the CMS, paralimbic regions involved in the processing of internal states such as the insula have also been suggested to play an important role in tasks requiring the processing of information relevant to the self (Craig, 2009; Modinos, Ormel, & Aleman, 2009). In fact, insula activation has been reported by many of the studies investigating self-reference (Farrer & Frith, 2002; Fink et al., 1996; Fossati et al., 2004; Gusnard et al., 2001; Johnson et al., 2005; Kircher et al., 2000; Moran, Heatherton, & Kelley, 2009; Ruby & Decety, 2001; Takahashi et al., 2008), and its role in self-reflection has been emphasized by recent reviews and meta-analyses (Schmitz & Johnson, 2007; van der Meer et al., 2010). The findings suggest that the insula's contribution is to mediate between a bodily orienting mechanism in response to ventral MPFC self-relevance detection and to provide the individual with further information on the internal bodily state, while an

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evaluation and a decision concerning the applicability of the stimulus to self is likely to be finalized by the dorsal MPFC (Northoff & Bermpohl, 2004; Northoff et al., 2006).

There is evidence to suggest that abnormalities in self-referential processing and underlying neural mechanisms are relevant to the expression of psychosis. Schizophrenia in particular has been conceptualized as a disorder of the self (Kircher & David, 2003; Parnas, 2000). Self-disturbance is thought to play a key role in the patients' maladaptive social functioning and in the genesis of positive psychotic symptoms such as hallucinations and delusions (Bentall, Corcoran, Howard, Blackwood, & Kinderman, 2001; Blackwood, Howard, Bentall, & Murray, 2001). Interestingly, CMS dysfunction has been reported in patients with schizophrenia across a variety of tasks involving self- and/or other-referential processing (theory of mind, Marjoram et al., 2006; determining the self-relevance of a descriptive phrase, Blackwood et al., 2004; reality monitoring, Vinogradov, Luks, Schulman, & Simpson, 2008), as well as during rest (Garrity et al., 2007; Whitfield-Gabrieli et al., 2009).

In healthy populations, imaging studies have most commonly used self-reflection paradigms by which subjects are presented with trait adjectives or sentences and are asked whether the trait or sentence applies to them. In patients with schizophrenia, the only study to date to use fMRI to examine self-reflection presented preliminary evidence of abnormalities in brain activation during the processing of information related to another person (Murphy et al., 2010). However, the authors did not restrict their search to CMS structures, which would nevertheless represent a primary focus of interest when investigating self-reflection in the brain (Northoff et al., 2006; van der Meer et al., 2010). In addition, the effect of the valence of the trait adjectives/sentences was not taken into account, although it reportedly has a differential effect on activation of CMS and insula (Fossati et al., 2003). Patients with schizophrenia are thought to display distorted attributions of positive and negative self-related information as a means of maintaining self-esteem (Bentall, Kinderman, & Kaney, 1994); thus, examining the effect of valence seems warranted. Overall, the state of current research regarding the neural correlates of impaired self-reflection in psychotic disorders is limited.

From a structural point of view, morphologic changes in CMS are among the earliest to occur in schizophrenia (Wright et al., 2000) and may precede the onset of frank psychosis (e.g., Borgwardt et al., 2007; Pantelis et al., 2003). In individuals at clinical risk of psychosis, not only the CMS but also the insular cortex appears to be compromised, reflecting a preexisting vulnerability (Borgwardt, Fusar-Poli, Radue, & Riecher-Rössler, 2008; Takahashi et al., 2009). Results in samples at clinical risk of psychosis thus converge with findings in patients to suggest a role of CMS and insular abnormalities in the pathophysiology of psychosis (Nelson et al., 2009). In fact, it has been recently proposed that disturbances in self-referential processing may represent a psychopathological trait marker of psychotic vulnerability, particularly of schizophrenia-spectrum disorders (Nelson, Yung, Bechdolf, & McGorry, 2008; Parnas, 2000, 2003; Sass & Parnas, 2003).

Schizotypy describes a continuum of personality characteristics and experiences related to psychosis in the general population (Claridge et al., 1996). Schizotypal traits are thought to constitute a range of enduring, biologically determined personality and cognitive traits that predispose to schizophrenia (Chapman, Chapman,

Kwapil, Eckblad, & Zinser, 1994; Lenzenweger, 2006; Meehl, 1962). Psychometric measures may be used to detect schizotypal traits in healthy people (Claridge, 1997; Lenzenweger, 1994; Stefanis et al., 2002). Prior research has demonstrated the validity of such measures as indicators of vulnerability to schizophrenia (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Horan, Blanchard, Clark, & Green, 2008) or, more generally, of *psychosis proneness* (PP) (Meyer & Hautzinger, 2002). PP is therefore conceptualized as a subclinical manifestation of the same underlying biological factors of schizophrenia-spectrum disorders (Gooding, Tallent, & Matts, 2005; Johns & van Os, 2001; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Research in PP has revealed impairments in measures of emotional, social, and cognitive functioning parallel to those of schizophrenia patients (Horan, Blanchard, Clark, & Green, 2008; Henry et al., 2009; Modinos, Ormel, & Aleman, 2010; Mohanty et al., 2005; van 't Wout, Aleman, Kessels, Larøi, & Kahn, 2004), especially associated with positive-dimension PP (e.g., unusual experiences, odd beliefs). Furthermore, in subjects with PP, symptoms of paranoid ideation have been associated with altered perceptions of the self (Martin & Penn, 2001). Differences in brain morphology have also been reported in such a sample, falling within the CMS (Modinos et al., 2010). An unresolved question is whether psychosis-prone individuals show differences in brain activation during self-reflective processing. Research on such a sample holds several strengths, as it allows for the study of psychotic experiences without the confounding factors of medication, illness duration, institutionalization, or other consequences of the clinical disorder.

The present study aimed to investigate brain activation associated with self-reflection in individuals with high as compared to individuals with low positive-dimension PP. In particular, we focused on the processing of self- and other-referential positive and negative personality trait sentences. Based on previous literature reporting associations between positive psychotic phenomena and increased CMS activity, and the role of the insula in self-reflective processing as well as in the pathophysiology of psychosis, we hypothesized that individuals with high levels of positive PP would show increased neural activation in the CMS and the insular cortex during self-reflection relative to subjects with low positive PP. We further envisaged that subjects with high PP would show differential brain activation in these regions relative to low PP when separately analyzing the response to positive and negative self-related stimuli.

Method

Participants

The recruitment procedure has been explained elsewhere (Modinos et al., 2010; Modinos, Ormel, & Aleman, 2010). In short, 600 undergraduate students were screened with the positive subscale of the Community Assessment of Psychic Experiences questionnaire (CAPE; Stefanis et al., 2002). They all gave written informed consent to complete the CAPE. According to their CAPE scores, 36 subjects were ultimately recruited for the actual fMRI experiment. Eighteen right-handed subjects scoring above the 75th percentile (as recommended by Konings, Bak, Hanssen, van Os, & Krabbendam, 2006) were assigned to the "high PP" group, and 18 right-handed subjects scoring below the 25th percentile of the

distribution were included in the “low PP” group. Table 1 summarizes the demographic data of the participants. Groups were matched for age, sex, handedness, and level of education. These subjects were screened for exclusion criteria using a self-report checklist for healthy subjects, comprising the following points: (a) no personal history of neurological or psychiatric illness, (b) no family history of psychotic or neurological illness in first-degree relatives, (c) no use of illicit substances, and (d) no changes in overall level of functioning, including academic performance over the past 6 months. All 36 participants gave written informed consent to participate in the fMRI experiment after receiving a detailed explanation of the experimental protocol, which was approved by the Medical Ethical Committee of the University Medical Center Groningen.

Psychosis Proneness Questionnaire

The CAPE was used to measure PP. This instrument was chosen based on the following characteristics: (a) good validity and reliability for the assessment of schizotypal features in the general population (Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005), (b) good concurrent validity with interview-based measures (Konings, Bak, Hanssen, van Os, & Krabbendam, 2006), and (c) developed and standardized on a Dutch population. A detailed description of its psychometric properties and administration procedure can be found elsewhere (Stefanis et al., 2002). In brief, this is a 42-item self-report questionnaire measuring lifetime frequency of attenuated psychotic symptoms, on a 4-point scale of “never,” “sometimes,” “often,” and “nearly always.” Konings et al. (2006) reported high effect sizes for the internal stability of the CAPE (0.6–0.8), indicating that self-reported dimensions of PP at baseline were strongly associated with the same dimensions at follow-up (mean interval, 7.7 months). Thus, the time lag between completion of the CAPE and fMRI scanning should not affect the findings.

The CAPE was originally based on a three-factor structure of positive, negative, and depressive factors. There is evidence to suggest that schizotypal traits fall into a factor organization similar to that in schizophrenia, consisting of positive (e.g., magical ideation, perceptual aberration), negative (e.g., physical anhedonia,

social anhedonia), and disorganized (e.g., disorganized speech and behavior) symptom constellations (Claridge et al., 1996; Kerns, 2006; Liddle, 1987). For the purpose of the present study, we only used the scores on the positive factor, given that a number of studies have reported a relationship between positive symptoms of psychosis and CMS disturbances (Borgwardt et al., 2007; Nelson, Yung, Bechdolf, & McGorry, 2008; Pantelis et al., 2003; Wright et al., 2000). Thus, we measured positive factor PP (e.g., unusual experiences, odd beliefs), which is thought to relate to the positive dimension of the schizotypy concept (Claridge et al., 1996). Of note, the positive dimension of the CAPE is significantly correlated with the positive dimension of the Structured Interview for Schizotypy, Revised (SIR-R; $\beta = .52$, $t = 8.48$, $p = .000$), and the positive dimension of the Brief Psychiatric Rating Scale (BPRS; $\beta = .27$, $t = 3.54$, $p = .000$) (Konings, Bak, Hanssen, van Os, & Krabbendam, 2006).

Task

Two lists of 30 sentences containing a personality-trait adjective as keyword were constructed from Anderson’s list of personality-trait words (Anderson, 1968), which were shown to the participants during the scan acquisitions. Within each of the two lists, half of the keywords were positive and half were negative, selected from the top 20% and bottom 20%, respectively, of Anderson’s sample. One additional list of 10 sentences was used for practice trials. The study included three different judgment conditions: self-referential processing (“I am trustworthy”), other-referential processing (“OTHER is friendly”), and general semantic processing (used as baseline, control task). The semantic condition included 30 sentences about general knowledge, such as “You need water to live,” and “Spring comes after Autumn.” Sentences with positive traits, negative traits, and general knowledge were matched for semantic complexity and ease of understanding.

Procedure

Before scanning, a detailed explanation of the task was given to all subjects and they were asked to choose an acquaintance upon whom they were to reflect inside the scanner. An eligible acquaintance was defined as someone familiar to the degree of being able to judge their personality traits, but someone who was not too close and did not elicit strong feelings in them. Thus, subjects chose a relatively “neutral” other, such as a classmate or a teammate, and verbalized their choice to the researcher before scanning. All subjects in the study except one who chose a “neutral” teammate reported choosing “neutral” classmates.

The scanning paradigm has been described elsewhere (Modinos, Ormel, & Aleman, 2009). In brief, the task included three different judgment conditions. In the self-reference condition, participants judged whether or not each sentence was true about them. In the other-reference condition, participants judged whether or not each sentence was true about their chosen acquaintance. Subjects were not required to judge the valence itself. In the semantic condition, participants judged whether or not a sentence was true about general knowledge. This condition was used to control for visual and motor processing of stimuli, language processing, and type of judgment. Task administration followed that used in the original study, using this paradigm to investigate self-reflection in the brain

Table 1
Demographic and Behavioral Data for the High and Low Psychosis Proneness Groups

Variable	Low PP ($n = 18$)	High PP ($n = 18$)
Mean (<i>SD</i>) age (years)	20.8 (2.3)	19.8 (1.8)
Gender (males/females)	10/8	10/8
Mean (<i>SD</i>) CAPE score	1.13 (.03)	1.73 (.12)
Mean (<i>SD</i>) RTs		
Positive self	1855 (319)	1723 (309)
Negative self	1969 (231)	1855 (245)
Positive other	1953 (314)	1837 (291)
Negative other	2030 (258)	2008 (293)
Semantic	1943 (238)	1883 (330)

Note. There were no significant differences in age ($p = .157$) or gender ($p = 1$). High PP subjects had higher CAPE scores than low PP ($p < .001$). CAPE = Community Assessment of Psychic Experiences; PP = psychosis proneness; RT = reaction time; *SD* = standard deviation.

(Johnson et al., 2002). Order of presentation of the three conditions was counterbalanced across subjects, and sentences of positive and negative valence were randomly presented in each block of the “self” and “other” conditions. The experimental design consisted of a total of 90 trials, divided into 5 blocks of 24 s. In each block, 6 different sentences of the same condition (Self, Other, Semantic) were presented for 4 s each. Blocks were interleaved with four 20-s rest periods, consisting of a fixation cross-presented in the middle of the screen (at the beginning, two in the middle, and at the end of experiment).

There was an equal number of true/false items in the semantic condition (50% of each) so that results would not be confounded by this effect. Subjects responded to each statement, presented in white letters on a black screen, with a “yes” (right hand, index finger) or “no” (right hand, middle finger) button-press response. A constant visual reminder of which button to press was displayed at the bottom of the screen throughout the entire scanning session.

The experiment was executed using a Pentium PC using the software package E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA). Stimuli were projected onto a screen positioned at the end of the bore, visible through a mirror attached to the head coil. Cushions were used to minimize head movement.

Imaging Data Acquisition and Preprocessing

Images were acquired in a 3-T Philips Intera magnetic resonance scanner (Philips Medical Systems, Best, the Netherlands). Functional data comprised 246 volumes acquired with T2*-weighted gradient echo planar imaging (EPI) sequence, using a sense-8 head coil. Thirty-seven slices per volume, sensitive to blood oxygenation level-dependent (BOLD) contrast, were obtained using a TR of 2 s, flip angle = 70°, TE = 35 ms; in-plane resolution = 3.5 × 3.5 mm; and field of view of 224 mm. Slices were acquired interleaved and oriented parallel to the AC-PC plane, with a thickness of 3.5 mm and no gap. High-resolution T1-weighted 3D fast-field echo sequences were obtained for anatomical reference (160 slices, TR of 25 ms, TE = 4.6 ms, slice-thickness = 1 mm; matrix: 256 × 256; field of view = 26 cm; voxel size = 1 × 1 × 1 mm).

Functional data were preprocessed using SPM5 software (<http://www.fil.ion.ucl.ac.uk/spm>). All functional images were slice-time corrected and realigned. After realignment, the obtained mean EPI image was coregistered with the structural T1 image. Subsequently, images were spatially normalized to the standard stereotaxic space defined by the Montreal Neurological Institute (MNI) template. During normalization, scans were resampled onto a 2 × 2 × 2 mm³ grid. Functional images were spatially smoothed with a 3D isotropic Gaussian kernel (FWHM of 8 mm). Low-frequency noise was removed by applying a high-pass filter (cutoff of 128 s) to the fMRI time-series at each voxel.

Statistical Analysis

We used SPSS for analysis of behavioral data. If Levene’s test for equality of variances revealed significance, corrections of the degrees of freedom as well as the *p* values (Greenhouse-Geisser) were reported. We assessed subjects’ attributional style of personality traits according to valence by computing the individual number of “Yes” responses to each condition (positive self, negative

self, positive other, negative other). Attributional style and reaction times (RT) were examined with a repeated measures ANOVA, with the within-subject factor “Condition” (positive self, negative self, positive other, negative other) and the between-subjects factor “Group” (low PP, high PP). Post hoc analyses of significant effects were performed by *t* tests (Bonferroni corrected for multiple comparisons).

For the fMRI data, single-subject statistics of the different event types (positive self, negative self, positive other, negative other) versus the semantic baseline were defined as contrasts using SPM5. The resulting intrasubject contrast images were entered into a group analysis consisting of a mixed-effect three-factor ANOVA with “Subject” as random factor, “Group” as between-subjects factor, and “Condition” (positive self > semantic, negative self > semantic, positive other > semantic, negative other > semantic) as within-subject factor. Given our a priori hypothesis of a critical role of the CMS and insula based on the literature in self-reflective processes (Northoff et al., 2006; van der Meer et al., 2010), and in psychotic vulnerability (Nelson et al., 2009), we restricted our search to these structures by applying a predefined anatomical mask to all analyses. The mask included the MPFC (superior medial gyrus), ACC, PCC, and insula (all bilateral), as provided by the Anatomical Automatic Labeling (AAL) software using the WFU_PickAtlas toolbox in SPM5. We first tested the effects of self > semantic, other > semantic, self > other, and other > self separately in each group (within-group analysis) to subsequently examine between-group differences in these contrasts. For the sake of completeness, based on previous research highlighting the relevance of valence effects when processing self-referential information (Fossati et al., 2003), the design allowed for the examination of putative differential valence effects between groups [for example, Low PP (positive self > semantic) > High PP (positive self > semantic)]. In all analysis, effects were tested by applying an initial voxel-wise threshold of *p* < .001 uncorrected, with extent threshold of 5 voxels. Activations were then considered significant at a threshold of *p* < .05, False Discovery Rate (FDR) corrected for multiple comparisons. Brain structure labeling was performed using the AAL Toolbox for SPM (Tzourio-Mazoyer et al., 2002).

Finally, parameter estimates of significant clusters of between-groups activations were extracted using the Marsbar toolbox in SPM5 in order to test for associations between CAPE score, brain activity, and behavior (attribution of personality traits), by conducting Pearson’s correlation analysis in SPSS (two-tailed).

Results

Behavioral Data

With regard to the demographic data, both groups included an equal number of men and women, and there were no significant differences between the groups relating to age, $F(1, 34) = 2.093$, $p = .157$. Scores on the CAPE were significantly higher in the High PP group than in the Low PP group, $F(1, 34) = 381.324$, $p < .001$ (see Table 1).

Attributional style of personality traits. Analysis of attributional style revealed a significant main effect of “Condition,” $F(3, 90) = 247.411$, $p < .001$, by which there was more self-attribution of positive traits than negative ones, $p < .001$, more other-attribution of positive traits than negative ones, $p < .001$,

and more self-attribution of positive traits than other-attribution of negative traits, $p < .001$. There was no main effect of Group, $F(1, 30) < 1$, *ns*. However, there was a significant “group \times condition” interaction, $F(3, 90) = 3.964$, $p = .011$. Post hoc analyses revealed that high PP individuals attributed significantly less positive traits to other than low PP subjects ($p = .014$). These results are shown in Figure 1.

There were no significant between-group differences in response accuracy for the Semantic condition, $F(1, 35) = 2.122$, $p = .154$.

Reaction times. A repeated measures ANOVA with “Condition” as within-subject factor and “Group” as between-subjects factor revealed a significant main effect of “Condition”, $F(3, 90) = 7.721$, $p < .001$. Post hoc analysis of RT revealed the following significant pairs: positive self versus negative other ($p < .001$), negative self versus negative other ($p = .017$), and positive other versus negative other ($p = .036$). Thus, subjects were slowest on judging negative traits related to other. There was no main effect of “Group”, $F(1, 30) < 1$, *ns*, or significant “group \times condition” interaction, $F(3, 90) = 1.541$, $p = .209$. Table 1 displays demographic and RT data of the two groups.

Correlation analysis between CAPE scores and attribution of personality trait sentences revealed a significant negative correlation between CAPE score and attribution of positive traits to other ($r = -.460$, $p = .008$), so that higher scores in the CAPE were associated with less attribution of positive traits to other.

Functional Imaging Results

Within groups, self-reflection produced increased activation within the CMS (MPFC, ACC, PCC) and insula relative to the semantic baseline. Other-reflection also induced activation in the CMS relative to the semantic condition, except in the insula.

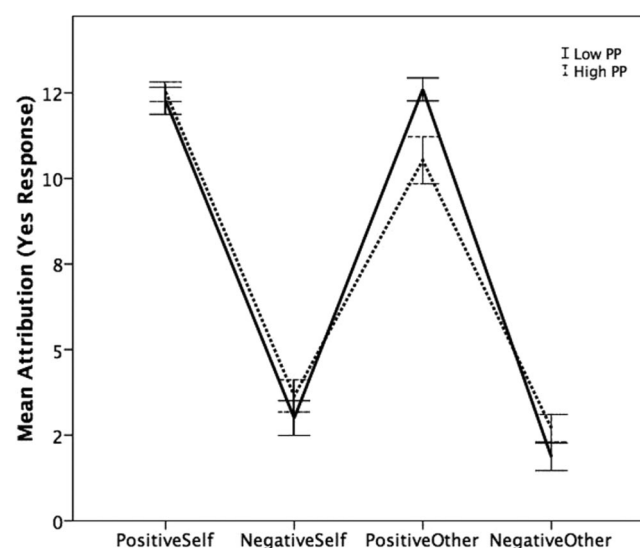


Figure 1. Behavioral results of the task paradigm. Significant group \times condition interaction, showing a significantly less attribution of positive items to other in subjects with high positive dimension psychosis proneness (High PP) relative to the low psychosis-prone group (Low PP). Error bars depict standard error of the mean.

Further, the contrast self $>$ other revealed stronger activation in anterior CMS (ACC, vMPFC) together with the insula in both groups. Finally, the low PP group showed stronger activation of PCC/Precuneus to other $>$ self, whereas in the high PP group this contrast did not induce significant activation (Table 2, Table 3, and Figure 2).

Between-groups analysis revealed no significant differences for the following contrasts: other $>$ semantic, self $>$ other, or other $>$ self. There was a trend toward stronger activation of the left insula in high PP subjects for self $>$ semantic, which was significant at $p < .001$ uncorrected (Table 4, Figure 3).

Next, we examined group differences separately for sentences of positive and negative valence. These analyses revealed that the high PP group showed stronger activation in the left insula, right dMPFC, and left vMPFC for the contrast of positive self $>$ semantic. For the contrast negative self $>$ semantic, high PP subjects showed stronger activation than low PP in bilateral insula, ACC, and right dMPFC (Table 4, Figure 3). There were no significant between-group differences in the contrasts positive other $>$ semantic or negative other $>$ semantic.

Finally, parameter estimates of clusters showing significant between-group differences in activation were subjected to correlation analysis with the CAPE positive-factor scores. There was a significant positive correlation between CAPE and left vMPFC ($r = .415$, $p = .012$), left insula ($r = .364$, $p = .029$), and a trend with right dMPFC ($r = .328$, $p = .051$). Cook's D test was applied to rule out the influence of potential outliers on the correlations. This correction strengthened the significance of the correlations (left vMPFC, $r = .577$, $p < .001$; left insula, $r = .476$, $p = .005$; right dMPFC, $r = .529$, $p = .002$; see Figure 4).

Discussion

The goal of this study was to examine whether individuals with high levels of positive-dimension PP would show differences in cerebral activation during self-reflective processing relative to subjects with low levels. Behaviorally, individuals with high positive PP significantly attributed less positive items to other than subjects with low positive PP. At the brain level, both groups showed robust activation increases in CMS and insula when judging whether a personality trait sentence applied to self relative to the semantic baseline (self $>$ semantic). When reflecting upon sentences related to other, both groups showed similar activation increases in the CMS, except in the insular cortex. In addition, both groups showed stronger activation of a cluster comprising the anterior portion of the CMS as well as the insula for self versus other, consistent with prior literature on the neural correlates of self-reflective processing (van der Meer et al., 2010). The contrast other $>$ self induced activation in PCC in participants with low PP, consistent with a previous study in healthy individuals (Modinos, Ormel & Aleman, 2009). However, other $>$ self did not elicit significant activation in individuals with high positive PP. Between-group comparisons revealed a trend toward stronger activation of the left insula during self $>$ semantic in high PP individuals ($p < .001$, uncorrected). In addition, trait valence had a differential effect between groups. High PP individuals showed increased activation in the left insula, right dMPFC, and left vMPFC when

Table 2

Coordinates and T Scores (False Discovery Rate Corrected for Multiple Comparisons, $p < .05$) for Within-Group Effects in Subjects With Low Psychosis Proneness

Region	L/R	MNI Coordinates			T-score	Size
		x	y	z		
Self > Semantic						
ACC	L	-8	52	-2	13.80	4105
dMPFC		-4	58	22	10.71	
PCC	L	-6	-52	26	13.00	523
Insula	L	-34	18	-12	4.92	100
	R	32	18	-16	3.51	9
Other > Semantic						
PCC/Precuneus		4	-58	30	19.20	656
dMPFC	L	-6	58	26	12.00	2287
vMPFC		-2	64	4	8.57	
ACC	L	-8	52	-2	7.70	
Self > Other						
ACC		-2	42	6	5.64	1078
Insula	L	-40	20	4	3.50	30
	R	44	18	-6	3.15	45
vMPFC	L	-12	54	2	3.34	10
Other > Self						
PCC/Precuneus		4	-58	30	6.58	310

Note. Coordinates are in Montreal Neurologic Institute (MNI) space. R = right hemisphere; L = left hemisphere; size = no. of activated voxels; ACC = anterior cingulate cortex; dMPFC = dorsal medial prefrontal cortex; vMPFC = ventral medial prefrontal cortex; PCC = posterior cingulate cortex.

processing self-related stimuli of positive valence, and in bilateral insula, right dMPFC, and ACC when self-related stimuli were of negative valence.

Prior behavioral studies have reported cognitive biases in patients with schizophrenia while processing information related to self. In particular, patients may display distorted attributions of positive and negative traits or events to self and other, a mechanism that is thought to serve the function of maintaining self-esteem (Bentall, Kinderman, & Kaney, 1994). Current theoretical views propose that dysfunctional strategies for avoiding low self-esteem are thought to underlie positive psychotic symptoms, such as paranoia-inducing explanations (Bentall et al., 2001; Bentall, Kinderman, & Kaney, 1994). Our finding that individuals with high positive PP exhibited biased attribution of personality traits seemingly supports this idea, which is further emphasized by the negative correlation between CAPE positive-factor scores and attribution of positive traits to other across the whole sample. This evidence expands previous reports of altered self-referential processing in PP within other domains (e.g., self-face perception; Gallup, Anderson, & Platek, 2003; Larøi, D'Argembeau, Brédart, & van der Linden, 2007; Platek & Gallup, 2002; Platek, Myers, Critton, & Gallup, 2003).

Although a recent comprehensive meta-analysis highlighted that only a handful of neuroimaging studies have examined brain activation associated with other-reflection relative to self-reflection (other > self contrasts; van der Meer et al., 2010), it has been documented that this is associated with activation in regions within the posterior CMS, that is, PCC and precuneus (Modinos, Ormel, & Aleman, 2009). The PCC is thought to mediate autobi-

ographical memory, which is a relevant process for self- and other-reflection. In order to make an accurate decision on the applicability of a personality characteristic to self and other, autobiographical memory consultation is required, for it provides the individual with further past information on the self and the other (van der Meer et al., 2010). Other-reflection requires accessing information that may be less readily accessible than that related to the self, which would require an increased cognitive effort based on drawing on autobiographical memories of past situations shared with the other that will aid in the decision. In the present study, increased PCC response during other-reflection was observed in subjects with low, but not in subjects with high, positive PP, the latter also showing less favorable judgments about the other person.

The high PP group showed a trend toward stronger activation in the left insula during self > semantic compared to low PP. Based on the known role of the insular cortex in processing the emotional value of stimuli (Phillips, Drevets, Rauch, & Lane, 2003), and in the processing of internal states (Craig, 2009), information relevant to self might induce stronger emotional and interoceptive response in subjects with high positive PP. These results are consistent with prior research in subjects with high positive PP reporting increased sensitivity to emotional material (Mohanty et al., 2005; van 't Wout, Aleman, Kessels, Larøi, & Kahn, 2004). This is particularly important because patients with positive-symptom schizophrenia tend to be more reactive to affective stimuli than patients with negative symp-

Table 3

Coordinates and T Scores (False Discovery Rate Corrected for Multiple Comparisons, $p < .05$) for Within-Group Effects in Subjects With High Psychosis Proneness

Region	L/R	MNI Coordinates			T-score	Size
		x	y	z		
Self > Semantic						
ACC		-4	44	2	9.50	4042
vMPFC	L	-12	54	4	9.26	
		2	52	4	8.51	
PCC/Precuneus		4	-58	30	9.45	347
Insula	R	30	16	-16	4.37	36
	L	-30	18	-16	3.96	46
dMPFC	L	-10	38	52	4.31	32
Other > Semantic						
PCC/Precuneus		4	-58	30	13.63	582
vMPFC		4	62	6	6.55	1160
dMPFC	L	-8	60	20	5.87	
ACC	L	-10	46	4	4.91	
Self > Other						
ACC		-2	42	10	4.18	280
vMPFC		4	50	2	3.57	
Insula	R	42	10	-4	3.26	58
	L	-40	10	-8	2.88	35
Other > Self						
None						

Note. Coordinates are in Montreal Neurologic Institute (MNI) space. R = right hemisphere; L = left hemisphere; size = no. of activated voxels; ACC = anterior cingulate cortex; dMPFC = dorsal medial prefrontal cortex; vMPFC = ventral medial prefrontal cortex; PCC = posterior cingulate cortex.

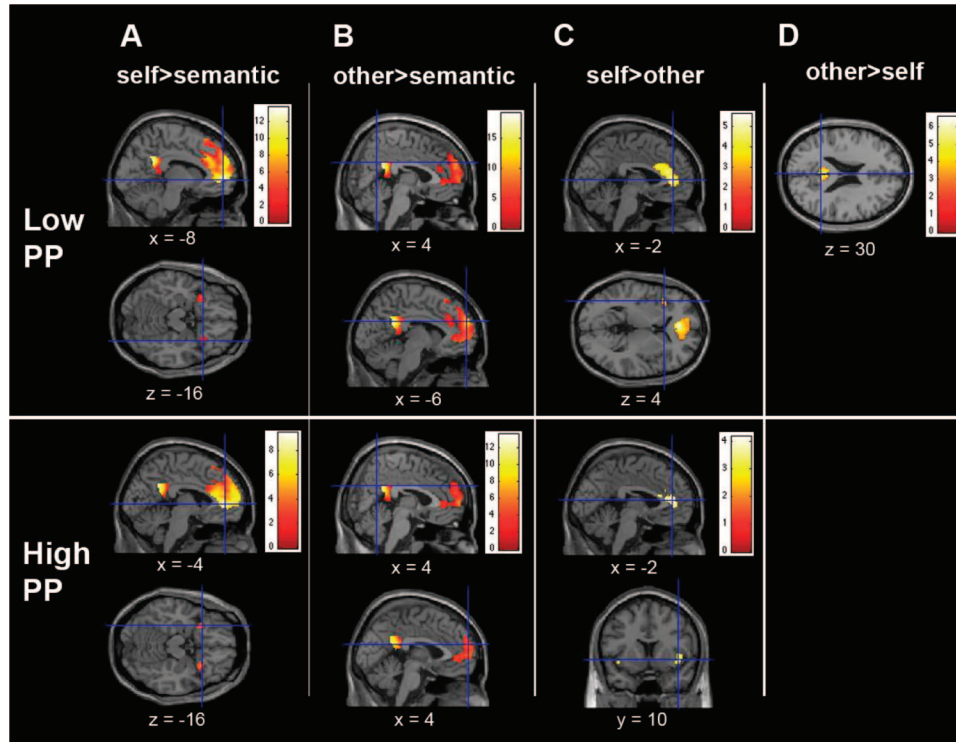


Figure 2. Brain areas showing significant effects within groups during self-reflection relative to semantic baseline (A), other-reflection relative to baseline (B), self-reflection relative to other-reflection (C), and other-reflection relative to self-reflection (D) ($p < .05$, false discovery rate corrected). Coordinates of activated regions may be found in Tables 2 and 3.

toms (Docherty, Evans, Sledge, Seibyl, & Krystal, 1994). The absence of significant between-group differences in the CMS for self > semantic might seem counterintuitive. Nevertheless, there was significant activation in CMS within groups for that

Table 4

Coordinates and T Scores (False Discovery Rate Corrected for Multiple Comparisons, $p < .05$) for Cerebral Areas Significantly More Activated in the Group Comparison High Psychosis-Prone > Low Psychosis-Prone

Region	L/R	MNI Coordinates			T-score	Size
		x	y	z		
Self > Semantic						
Insula	L	-34	4	12	3.80	22
Positive Self > Semantic						
Insula	L	-34	4	12	4.89	125
dMPFC		12	52	24	4.35	60
vMPFC		-4	66	14	4.24	69
Negative Self > Semantic						
Insula	R	42	6	10	4.22	80
	L	-34	4	12	3.80	30
ACC		14	30	20	3.53	22
dMPFC		10	56	26	3.45	10

Note. Coordinates are in Montreal Neurologic Institute (MNI) space. R = right hemisphere; L = left hemisphere; size = no. of activated voxels; ACC = anterior cingulate cortex; dMPFC = dorsal medial prefrontal cortex; vMPFC = ventral medial prefrontal cortex; PCC = posterior cingulate cortex.

contrast, indicating that findings were indeed located in those regions. Differences between high and low PP associated with self-referential processing might pertain more to the domain of areas involved in emotional processing and bodily awareness rather than in general self-reflection.

Another relevant finding is that additional differences in neural activation were observed between groups when investigating valence effects. Subjects with high positive PP showed stronger activation in the left vMPFC, right dMPFC, and left insula for positive self-related stimuli. When the material was of negative valence, the response in the right dMPFC and the left insula was also greater than in low PP, together with the ACC. With a similar task, Fossati et al. (2003) reported increased activation of the insula and the dMPFC to self-related emotional traits in healthy individuals. They suggested that in order to avoid feeling emotional and maintain a self-protective mode, subjects might have attempted to inhibit their emotional responses during the processing of self-related words. In our study, both groups activated the insula and dMPFC to self-related sentences. High PP individuals, however, activated these regions to a greater extent. Mohanty et al. (2005) reported increased prefrontal activation in subjects with high positive PP during maintenance of the attentional set in the presence of emotional distractors, which was interpreted as greater cognitive effort in order to inhibit the response to emotional distractors. In addition, Modinos, Ormel, and Aleman (2010) also described greater activation within the PFC in high PP while subjects reappraised an emotional experience.

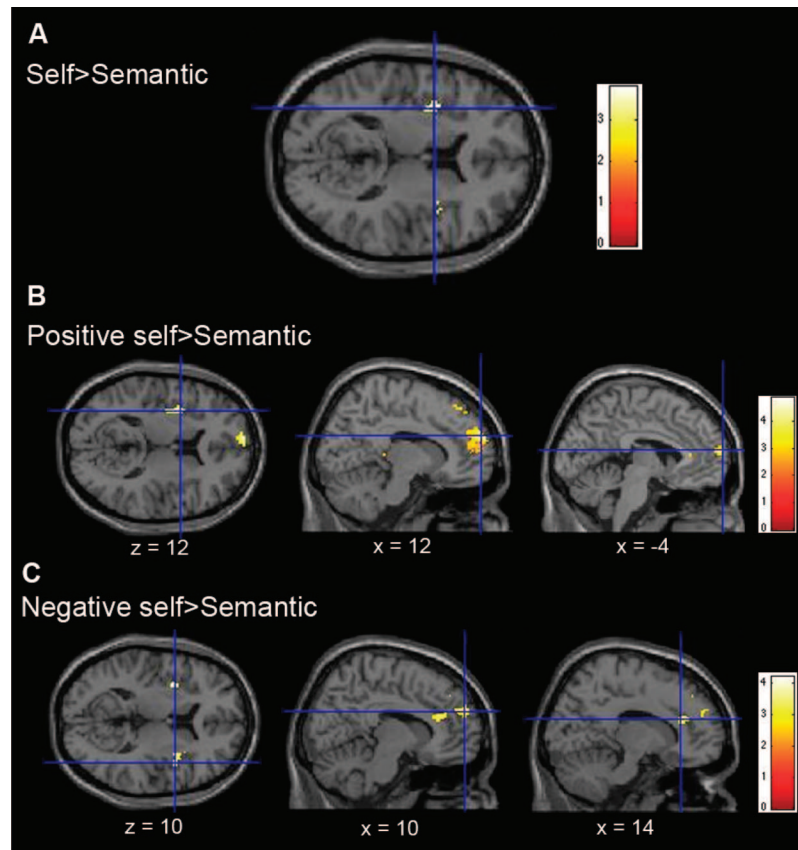


Figure 3. Panel A depicts brain areas showing significant stronger activations during self-referential processing, irrespective of valence, in subjects with high positive dimension psychosis proneness (PP) relative to subjects with low PP ($p < .05$, false discovery rate corrected). Panel B depicts brain areas showing significantly stronger activations during positive self-referential processing in high PP, and Panel C during negative self-referential processing. Coordinates of activated regions may be found in Table 4.

Furthermore, the ACC and the vMPFC were more strongly activated in high PP individuals for negative and positive sentences, respectively. The ACC is a key player in cognitive control and self-directed attention (van der Meer et al., 2010), in the integration of internal states with external information (Critchley, 2005), and in emotion processing and regulation (Lane et al., 1998; Mohanty et al., 2007). In the task context of evaluating self-related information, the dMPFC and the ACC, which communicate with the paralimbic structures (i.e., insula) and the vMPFC, represent a suitable network for integrating cognitive processing with emotional reactions and experience. In line with this previous evidence and that from prior studies in PP, the present results suggest that subjects with high PP might have an increased emotional response to self-related stimuli of positive and negative valence (activity in insula, vMPFC), which is seemingly associated with attempts to diminish this response (activity in dMPFC and ACC).

Of note, medial prefrontal regions including the ACC are known to be active during both resting state and self-referential processing (Gusnard, Akdubak, Shulman, & Raichle, 2001; Northoff et al., 2006; Lou et al., 2004). During resting state, hyperactivation and hyperconnectivity of CMS have been reported in schizophrenia (Garriety et al., 2007; Zhou et al., 2007), as well as in subjects at

genetic risk (Whitfield-Gabrieli et al., 2009). This has been interpreted as reflecting an enhanced focus in one's own thoughts and feelings, and greater CMS activity has been proposed to contribute to the positive symptoms and disturbances of thought that characterize schizophrenia (Whitfield-Gabrieli et al., 2009). Interestingly, a recent review of the literature on self-disturbance in schizophrenia and at-risk populations (Nelson et al., 2009) postulated that (a) CMS are involved in supporting a sense of self, (b) their dysfunction may be related to positive psychotic symptoms, and (c) changes thereof might be observed already in association with vulnerability to psychosis. The present findings lend empirical support to this proposal. Furthermore, the CMS and insula appear to have an important predictive value regarding later transition to psychosis (for review, see Smieskova et al., 2010; Wood et al., 2008).

Groups were formed with high and low scorers to allow consistency with previous literature on PP, which has typically compared performance between groups selected upon the same criterion (e.g., van 't Wout et al., 2004; Langdon & Coltheart, 1999, 2001, 2004; Jahshan & Sergi, 2007; Fernyhough, Jones, Whittle, Waterhouse, & Bentall, 2008; although see Janssen et al., 2006). The distribution of PP in nonclinical samples does not show a

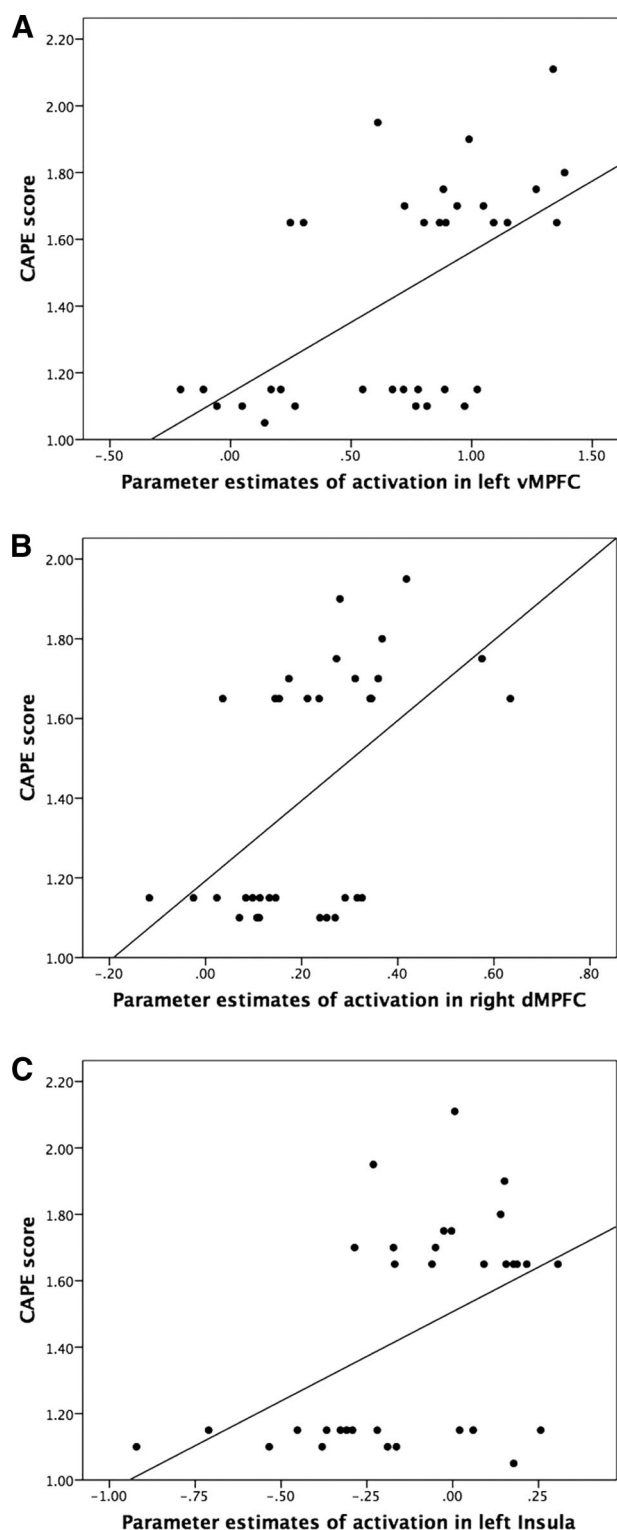


Figure 4. Scatterplots showing the positive relationships between individual scores in Psychosis Proneness (as assessed with the Community Assessment of Psychic Experiences, positive factor) and neural activation in (A) the left ventral medial prefrontal cortex (vMPFC), (B) the right dorsal medial prefrontal cortex (dMPFC), and (C) the left insula.

continuous normal distribution, but a continuous half-normal distribution, with the majority of the population having very low values, albeit a significant proportion also has progressively higher values (van Os et al., 2009). In addition, compared to other measures of PP (e.g., Paranoia Scale, Launay-Slade Hallucination Scale), the CAPE comprises more “pathological” items (e.g., does not tap on phenomena such as daydreaming), so that very low scores are “normal.” Thus, using average scorers would not be expected to significantly alter the present findings. However, future studies on PP including such a control group should help extend our findings. Another potential limitation of the present study is that participants were recruited from a university sample; thus, caution should be used when extrapolating the present findings to the general population. Of note, students function at a high level (Meehl, 1962); thus, psychosis-prone individuals with high intellectual capacity might cope better with the problems associated with PP (van ‘t Wout et al., 2004; Romme, Honig, Noort-hoorn, & Escher, 1992). This study used a self-report checklist for research on healthy subjects to rule out personal and family history of neurological or psychiatric illness. Complementing with a clinician-based instrument could have made the findings more compelling. Finally, future studies including an additional control condition with “neutral” self-related words, as far as possible, may expand the present findings. Nevertheless, our findings are encouraging for further behavioral and imaging work in such a group, which may help further expand the notion that self-disturbance may precede the onset of florid psychotic symptoms.

In conclusion, the present study reports differential attributional style of personality traits in subjects with high positive PP and differential patterns of brain activation in relevant regions (CMS, insula) during such mental activity. The cerebral areas in which between-group differences were detected appeared to be areas whose heightened activation has been previously documented in patients with schizophrenia, in genetic high-risk samples, and in association with positive psychotic symptoms. The current findings converge with prior evidence that self-related alterations may reflect pathophysiological mechanisms associated with psychotic experiences, rather than developing uniquely as a result of illness duration or long-term antipsychotic medication (Nelson et al., 2009; Nelson, Yung, Bechdolf, & McGorry, 2008).

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